Acceptance Criteria for Confirmation of Identity of Chemical Residues using Exact Mass Data within US FDA Office of Foods and Veterinary Medicine

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Background

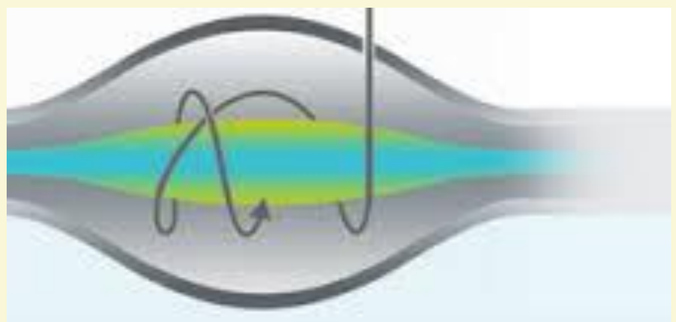
The Office of Foods and Veterinary Medicine (OFVM) of the US Food and Drug Administration has developed acceptance criteria for the confirmation of identity of chemical residues using exact mass data collected with high resolution mass spectrometry (HRMS). With recent technical advances in HRMS and its increased use in the analysis of foods and veterinary medicines, it was important to develop guidance so that users of HRMS are consistent in evaluating and comparing results for regulatory use. These criteria are meant to supplement the 2002 FDA Center for Veterinary Medicine (CVM) published Guidance for Industry (#118) titled "Mass Spectrometry for Confirmation of the Identity of Animal Drug Residues".

Scope

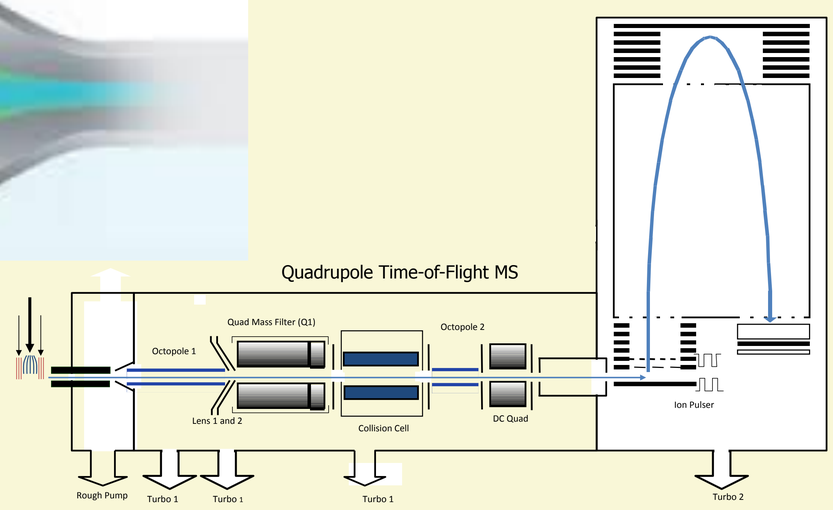
This guidance is applicable for the confirmation of identity of chemical residues using HRMS within the FDA FVM program, including but not limited to the following applications:

- The confirmation and identification of small molecules with a molecular weight range typically less than 1000 Daltons at residual levels. Such chemicals include veterinary drugs, pesticides, dyes, food or feed additives, and other natural or synthetic contaminants.
- The applicable matrices include foods of animal and plant origin, animal and pet feeds, ingredients used in the preparation of foods and feeds, dietary supplements, cosmetics, and other FDA regulated commodities that fall within the purview of OFVM.
- The primary focus is the use of HRMS for targeted analysis when the comparison standard is available, although aspects of non-targeted analysis are discussed.
- Other uses of HRMS in support of regulatory actions within the OFVM

High Resolution Mass Analyzers



Orbitrap Mass Analyzer



Confirmation Criteria

Mass Extraction Window (MEW):

- In full scan mass spectrometric measurements using HRMS, the selectivity for a particular analyte is determined by the narrowness of the mass extraction window (MEW) that is used to obtain the extracted ion chromatogram (EIC) of the target analyte.
- MEW has to be selected by careful consideration of the resolution of the instrument, drift of the mass axis and the complexity of the matrix.
- It is recommended that the optimum MEW be established with the standards in matrix using the same chromatographic and sample preparation procedures used in the method.

Signal Requirement:

- EIC generated with narrow MEW can produce baselines free of any visible noise. Calculation of signal-to-noise (S/N) ratio is not feasible under such conditions. If there is noise, then a S/N threshold ≥ 3 is recommended.
- Another way to set up a confidence or significance threshold is to use relative signal intensity, acquired from test sample vs. a comparison standard.

Retention time:

- The retention time must match contemporary standard ≤ 0.2 min, or ± 2.5% (not to exceed 0.5 min), or within experimental error established in the validated method (not to exceed 0.5 min).
- The EICs of two or more ions from an analyte using the same MEW must co-elute.

Mass accuracy:

For confirmation of identity, the measured exact mass of at least two ions (preferably structurally significant fragment or product ions in addition to precursor ion) should have a mass accuracy of ≤ 5 ppm in the MS^1 mode and ≤ 10 ppm in the MS/MS mode, as is calculated by:

$$\textit{Mass accuracy (ppm)} = [\textit{Measured mass} - \textit{calculated mass}]/\textit{calculated mass} \times 10^6$$

Ion Ratio:

- If the measured exact mass from two or more ions match the mass accuracy criterion, it is not necessary to calculate and report ion abundance ratios.
- If, however, the measured mass error is greater than the mass accuracy criterion, the ion ratio criteria for nominal mass data as described in CVM guidance 118 or ORA-LAB010 shall apply.

Summarized Requirements for Confirmation of Identity

MS mode	MS^1	MS/MS	MS^1 and MS/MS
EIC: signal requirement (absolute)	S/N greater ≥3, or an intensity ratio relative to the comparison standard equal or above a preset threshold		
EIC: retention time (relative to comparison std)	≤ 0.2 min, or within 2.5% (not to exceed 0.5 min), or within an established error range, (not to exceed 0.5 min)		
MS: Number of structurally significant ions	minimum 2	minimum 2	minimum 2 combined
MS: mass accuracy	≤ 5 ppm	≤ 10 ppm	MS^1 ≤ 5 ppm; MS/MS ≤ 10 ppm

The guidance has been approved and is now available at:
http://www.fda.gov/ScienceResearch/FieldScience/ucm273423.htm